

REMARKS

In view of the above amendments and the following remarks, the Examiner is requested to allow claims 1-35, 67-101 and 144-149, the only claims pending and under examination in this application.

In the above amendments, Claims 1 and 67 have been amended to further clarify that the methods include a step of producing the nucleic acid to be sequenced. Claims 148 and 149 have been amended to further clarify the particular method of producing the nucleic acids, support being found at page 15, lines 1-14. As the above amendments introduce no new matter to the application, their entry by the Examiner is respectfully requested.

Claim Rejections – 35 U.S.C. § 103(a)

In the advisory action, the rejection of Claims 1-34, 67-100, and 144-147 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Baldarelli et al. (U.S. Patent No. 6,015,714) in view of Kool (U.S. Patent 5,714,320). This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed method. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations (MPEP § 2143). The teaching or suggestion to arrive at the claimed method and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (MPEP § 2143 citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

Baldarelli et al. is silent with respect to the improvement in sequencing achieved by generating nucleic acid polymers having repeats. A reading of Baldarelli et al. would not provide the reader with any reason to use repeats. The primary emphasis of Baldarelli et al. is the method of sequencing, a method that does not involve chemical or enzymatic reactions. Baldarelli et al. notes that his

method is faster and can sequence longer nucleic acid polymers, but he is comparing his method with prior chemical and enzymatic methods. Baldarelli et al. devotes little disclosure to the structure of the nucleic acid polymer that is to be sequenced, and there is nothing in Baldarelli et al. regarding the influence of the structure of the polymer on the rate of sequencing. Examples 7 and 8 of Baldarelli et al. relate only to the feasibility of sequencing two different oligonucleotide homopolymers and an oligonucleotide heteropolymer, respectively, and not to the effect of the polymers on the rate of sequencing. Kool adds nothing regarding such an affect on the rate of sequencing, because Kool is not even directed to sequencing.

Only Applicant's disclosure provides a reason to use repeats. Moreover, unless one were using (improperly) Applicant's disclosure as a guide, there would have been no reason to select Kool's amplification method from among the many different methods known in the art for amplification.

In addition, Baldarelli et al. does not teach or suggest the use of modified bases, as specified Claims 1, 31-34, 67, 74, 75, 144, and 146, much less the specific types of modified nucleotides as specified in certain of the pending claims, and for the reasons set forth above provides no reason to use modified bases. Kool adds nothing to provide such a reason because Kool is not even directed to sequencing.

Significantly, neither Baldarelli et al. nor Kool teaches or suggests that using modified nucleotides reduces secondary structure that in turn increases the rate of nanopore sequencing, as in Applicant's invention. Applicant was the first to recognize the specific problem of the effect of secondary structure on the rate of nanopore sequencing, and then succeeded in solving that problem.

Recognition by Appellants of a problem in the art and solving that problem are themselves a basis for a determination of the unobviousness of Appellants' claimed invention:

"[Where] there is no evidence of record that a person of ordinary skill in the art at the time of [an applicant's] invention would have expected [a problem] ... to exist at all, it is not proper to conclude that [an invention] ... which solves this problem ... would have been obvious to that hypothetical person of ordinary skill in the art." *In re Peehs*, 612 F.2d 1287, 1290, 204 USPQ 835 (CCPA 1980) (citing *In re Nomiya*, 509 F.2d 566, 572, 184 USPQ 607, 612-13 (CCPA 1975))(emphasis added).

Furthermore, Applicant incorporates by reference herein his earlier arguments with respect to this combination of documents. Despite the fact that Baldarelli et al. is directed to a method of sequencing a nucleic acid polymer and Kool is directed to a method for synthesizing and amplification of DNA and RNA oligonucleotides, the Examiner's rationale for combining these two documents is that "the elements used in the synthesis of nucleic acid are the same [as in the present invention]." Final Office Action at page 3.

Applicant submits that the Examiner's rationale is insufficient to establish *prima facie* obviousness even if the elements disclosed by Kool are the same as those of Applicant. Applicant has pointed out earlier that the elements of Kool are not necessarily the same as those of Applicant. An element that allows selective cleavage, as disclosed in Kool, is not necessarily the same as a modified nucleotide that reduces secondary structure, as recited in present Claim 1, and no evidence to the contrary has been cited by the Office.

It is well-settled decisional law that the fact that the invention of a primary prior art reference *could* be modified to form the claimed invention would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); *In re Laskowski*, 871 F.2d 115, 10 USPQ2d 1397 (Fed. Cir. 1989). In *Environmental Instruments, Inc. v. Sutron Corp.*, 877 F.2d 1561, 11 USPQ2d 1132 (Fed. Cir. 1989), the court affirmed a combination of documents because the secondary reference plainly suggested the replacement of an aspect of the primary reference in order to arrive at the claimed invention. Therefore, the mere disclosure in a secondary document of the elements needed to arrive at Applicant's invention by modification of a primary document is insufficient to establish *prima facie* obviousness. Without a plain suggestion *in the cited art* to make such a modification, the modification exists only in Applicant's own disclosure, which is contrary to the case law and to MPEP § 2143. A rejection such as the present rejection, which is based only on the presence of the requisite elements in a secondary document, is evidence of quintessential hindsight, and not of *prima facie* obviousness. The two cited documents are sufficiently diverse so as not to suggest plainly the modification put forth by the Examiner.

In fact, Applicant further submits that Kool is not combinable with Baldarelli et al. because synthesis and sequencing of nucleic acids are sufficiently diverse as to be considered non-analogous. Therefore, the Examiner's earlier rationale (Office Action of August 30, 2005 at page 3) that "Kool is directed to efficient, low-cost and large scale synthesis of linear and circular oligonucleotide[s]" is immaterial because efficiency, low-cost, and the like do not alter the fact that Kool is directed to synthesis and Baldarelli et al. is not.

With respect to non-analogous art, the MPEP at § 2141.01(a) states:

'In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned.' *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). See also *In re Deminski*, 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986); *In re Clay*, 966 F.2d 656, 659, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992) ('A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem.');

Wang Laboratories Inc. v. Toshiba Corp., 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993); and *State Contracting & Eng'g Corp. v. Condotte America, Inc.*, 346 F.3d 1057, 1069, 68 USPQ2d 1481, 1490 (Fed. Cir. 2003) (where the general scope of a reference is outside the pertinent field of endeavor, the reference may be considered analogous art if subject matter disclosed therein is relevant to the particular problem with which the inventor is involved).

An inventor in the nucleotide sequencing art logically would not direct her attention to the nucleotide synthesis art, and one would expect that the problems encountered in the respective arts would be different.

Accordingly, for at least the reason that there would have been no motivation to combine the cited documents, there is no *prima facie* obviousness. Withdrawal of this rejection is respectfully requested.

Claims 35 and 101 stand finally rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Baldarelli et al. (U.S. Patent No. 6,015,714) in view of Kool (U.S. Patent 5,714,320) as applied above, and further in view of Thorp et al. (U.S. Patent No. 5,871,918). This rejection is respectfully traversed.

Thorp et al. was cited for its alleged teaching of a method of detecting a nucleic acid by using electron tunneling. Accordingly, Thorp et al. does nothing to remedy the deficiencies put forth *supra* of the combination of Baldarelli et al. and Kool. As such, for at least the reason that there is no motivation to combine the cited

documents, there is no *prima facie* obviousness. Withdrawal of this rejection is respectfully requested.

Finally, the Examiner entered a new ground of rejection in the Advisory Action, rejecting Claims 148 and 149 under 35 U.S.C. § 112, second paragraph. In view of the above amendments, it is believed that this rejection may be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone John Brady at (408) 553-3584.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10001492-2.

Respectfully submitted,

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